REMARKS

Entry of the foregoing and further and favorable examination of the subject application on the merits are respectfully requested and such action is earnestly solicited.

Claims 65-94 are currently pending in the present application. By the present amendment, claim 65 has been amended to delete the recitation of "monoclonal" and to add "library," in step (A) and to change "the" to "a" in step (C). Support for this amendment can be found, at least, in claim 1 as initially filed.

Applicants note that Claim 65 has been amended according to the Examiner's suggestion in a telephone interview with Applicants' undersigned representative on January 7, 2003.

Applicants gratefully acknowledge the courtesy shown by the Examiner to Applicants' undersigned representatives in telephone conversations on January 6 and 7, 2002. During these telephone conversations, the Examiner indicated her concern with the recitation of "monoclonal" antibody library in step (A) of Claim 1. Without conceding to the merits of this argument and solely in an effort to expedite prosecution, Claim 65 has been amended as agreed between the Examiner and Applicants' undersigned representative to delete the recitation of "monoclonal" in step (A). However, in the interest of assisting the Examiner in the understanding of the presently claimed invention, Applicants wish to clarify the issue concerning "monoclonal antibody libraries."

First, Applicants respectfully point out that Example 6 of the specification relates to the selection of three different antibodies to tumors from melanoma patients. The clone expressing one of these antibodies was initially at a frequency of 1 per 10 million clones. After three rounds of selection via the presently claimed invention, this frequency was increased to 1 per 10,000. The 10 million clones expressing antibodies constitutes a monoclonal antibody library.

Moreover, the language of the claim, which is directed toward the selection of an monoclonal antibody or antibody fragment, necessarily implies that the initial library must

contain such elements. Thus, the initial library can be considered a monoclonal antibody library or fragment library.

Finally, Applicants note that monoclonal antibody libraries are well-known in the art. In particular, the publications previously cited in the prosecution of this very application, notably the Cai publication (PNAS 92:6537-6541 (1995)) describes the use of monoclonal antibody libraries to isolate particular monoclonal antibodies. Applicants also submit herewith five review abstracts (Exhibits 1-5) for informational purposes demonstrating that monoclonal antibodies libraries are known in the art:

(Ex. 1) L.J. Garrard and E.A. Zhukovsky, "Antibody Expression in bacteriophage systems: the future of monoclonal antibodies?" *Curr. Opin. Biotechnol.* 3(5):474-80 (1992).

(Ex. 2) M.A. Persson, "Combinatorial libaries" *Int. Rev. Immunol.* 10(2-3):153-64 (1993).

(Ex. 3) R.J. Owens and R.J. Young, "The genetic engineering of monoclonal antibodies" *J. Immunol. Methods* 168(2):149-165 (1994).

(Ex. 4) B. Rapoport, et al., "Combinatorial libraries: new insights into human organ-specific autoantibodies" *Immunol. Today* 16(1):43-9 (1995).

(Ex. 5) D.L. Siegel, "Recombinant monoclonal antibody technology" *Transfus. Clin. Biol.* 9(1):15-22 (2002).

The foregoing amendments and remarks are made to place the application in better condition for examination and to assist the Examiner in the understanding of the presently claimed invention. A favorable action on the merits is respectfully requested.

If there are any other fees due in connection with the filing of this response, please charge the fees to Deposit Account No. 02-4800.

In the event that the Examiner has any outstanding issues, she is invited to contact the undersigned at her convenience.

Respectfully submitted,
BURNS, DOANE, SWECKER & MATHIS, L.L.P.

By: Jennifer Topmiller
Jennifer Topmiller, Ph.D.
Registration No. 50,435

P.O. Box 1404
Alexandria, Virginia 22313-1404
(703) 836-6620

Date: January 10, 2003

Attachment to Amendment and Reply dated January 10, 2003
Marked-up claim 65

65. (Amended) A method to acquire a monoclonal antibody or scFv/Fab fragments thereof against a target structure comprising the steps of:

(A) exposing a first mounted tissue to an initial [monoclonal] antibody library or scFv/Fab fragment library;

(B) eluting directly from the first mounted tissue unbound elements, wherein the unbound elements comprise a first enriched library;

(C) recovering a second enriched library comprising bound elements by cleaving the bound elements from the first mounted tissue such that [the] a monoclonal antibody or scFv/Fab fragment thereof remains bound to the first mounted tissue;

(D) amplifying either the first or second enriched libraries;

(E) repeating steps (A) to (B) to negatively enrich the unbound elements of the first enriched library or repeating steps (A) to (C) to positively enrich the bound elements of the second enriched library;

(F) exposing the negatively or positively enriched elements of step (E) to a second mounted tissue;

(G) eluting directly from the second mounted tissue unbound elements from the second mounted tissue, wherein the unbound elements comprise a third enriched library;

(H) recovering a fourth enriched library comprising second tissue section bound elements by cleaving the bound elements from the second mounted tissue such that the

monoclonal antibody or scFv/Fab fragment thereof remains bound to the second mounted tissue; and

(I) isolating an individual element from either the third or fourth enriched libraries, wherein the individual element is the monoclonal antibody or the scFv/Fab fragment thereof.

1: Curr Opin Biotechnol 1992 Oct;3(5):474-80 Related Articles, Links

Antibody expression in bacteriophage systems: the future of monoclonal antibodies?

Garrard LJ, Zhukovsky EA.

Genentech Inc, South San Francisco.

Bacteriophage systems have been utilized to express and isolate antibodies. This promising technology has been evolving rapidly and has the potential to revolutionize the way in which monoclonal antibodies are generated. This review focuses on the many recent advances that have been made in obtaining monoclonal antibodies from bacteriophage systems.

Publication Types:
- Review
- Review, Tutorial

PMID: 1368932 [PubMed - indexed for MEDLINE]

Display Abstract Show: 20 Sort Send to Text

1: Int Rev Immunol 1993;10(2-3):153-63

Related Articles, Links

Combinatorial libraries.

Persson MA.

Karolinska Institute, Department of Medicine, Karolinska Hospital, Stockholm, Sweden.

Combinatorial antibody libraries, in which PCR amplified immunoglobulin light and heavy chain DNA are randomly recombined irrespective of their pairing in vivo into a vector and subsequently expressed in E. coli, have quickly become a very productive tool to generate monoclonal antibodies from various species. It has been drastically improved by utilizing phage display technologies in the selection process of specific antibodies. A brief summary of current techniques, critical published experiments showing the versatility of these systems with emphasis on human antibodies and discussions on chain preference, affinity maturation and the advent of semisynthetic and non-immune libraries will be presented.

Publication Types:
- Review
- Review, Tutorial

PMID: 8360582 [PubMed - indexed for MEDLINE]

Display Abstract Show: 20 Sort Send Text

1: J Immunol Methods 1994 Feb 10;168(2):149-65 Related Articles, Links

The genetic engineering of monoclonal antibodies.

Owens RJ, Young RJ.

Calltech, Ltd., Berkshire, UK.

A number of recent technological developments have greatly facilitated the genetic engineering of immunoglobulins. The use of PCR has permitted the variable regions to be rapidly cloned either from a specific hybridoma source or as a gene library from non-immunised cells. The conversion of the rodent antibody into a humanized version is now well established. To develop these antibodies for clinical use has required the development of high level expression systems. For the expression of large multimeric glycoproteins, mammalian cell systems generally provide the highest levels of secreted product and therefore are the methods of choice for producing whole recombinant antibodies. Novel antigen-binding units have been developed by joining the two variable domains of an antibody into single-chain polypeptides. Such fragments can be produced in high yield by secretion from E. coli raising the prospect of bulk preparation of these antibody fragments for the development of low-cost immunopurification and assay reagents. Finally, the ability to screen for antigen binding by displaying immunoglobulin variable regions on the surface of filamentous bacteriaphages has opened up the possibility of bypassing the immune system to generate novel antibody specificities in vitro.

Publication Types:
- Review
- Review, Academic

PMID: 8308291 [PubMed - indexed for MEDLINE]

Entrez PubMed
Overview
Help | FAQ
Tutorial
New/Noteworthy
E-Utilities

PubMed Services
Journals Database
MeSH Browser
Single Citation Matcher
Batch Citation Matcher
Clinical Queries
LinkOut
Cubby

Related Resources
Order Documents
NLM Gateway
TOXNET
Consumer Health
Clinical Alerts
ClinicalTrials.gov
PubMed Central

Privacy Policy

1: Immunol Today 1995 Jan;16(1):43-9

SCIENCE DIRECT FULL-TEXT ARTICLE

Related Articles, Links

Combinatorial libraries: new insights into human organ-specific autoantibodies.

Rapoport B, Portolano S, McLachlan SM.

Thyroid Molecular Biology Unit, Veterans' Administration Medical Center, San Francisco, CA.

The recent application of immunoglobulin (Ig) gene combinatorial library technology has led to a logarithmic increase in information concerning human, disease-associated, organ-specific autoantibodies of the IgG class. As reviewed here by Basil Rapoport, Stefano Portolano and Sandra McLachlan, the molecular cloning, analysis and expression of the genes for increasing numbers of these human, monoclonal autoantibodies is providing new insight into the genetic background and epitopic repertoires of such molecules.

Publication Types:
- Review
- Review, Tutorial

PMID: 7533499 [PubMed - indexed for MEDLINE]

1: Transfus Clin Biol 2002 Jan;9(1):15-22

Recombinant monoclonal antibody technology.

Siegel DL.

Department of Pathology & Laboratory Medicine, University of Pennsylvania Medical Center, Room 510 Stellar-Chance Building, 422 Curie Blvd., Philadelphia, PA 19104, USA. siegeld@mail.med.upenn.edu

With the development of murine hybridoma technology over a quarter century ago, the ability to produce large quantities of well-characterized monoclonal antibody preparations revolutionized diagnostic and therapeutic medicine. For many applications in transfusion medicine, however, the production of serological reagents in mice has certain biological limitations relating to the difficulty in obtaining murine monoclonal antibodies specific for many human blood group antigens. Furthermore, for therapeutic purposes, the efficacy of murine-derived immunoglobulin preparations is limited by the induction of anti-mouse immune responses. Technical difficulties inherent in human hybridoma formation have led to novel molecular approaches that facilitate the isolation and production of human antibodies without the need for B-cell transformation, tissue culture, or even immunized individuals. These technologies, referred to as 'repertoire cloning' or 'Fab/phage display', involve the rapid cloning of immunoglobulin gene segments to create immune libraries from which antibodies with desired specificities can be selected. The use of such recombinant methods in transfusion medicine is anticipated to play an important role in the development and production of renewable supplies of low-cost reagents for diagnostic and therapeutic applications.

Publication Types:
- Review
- Review, Tutorial

PMID: 11889896 [PubMed - indexed for MEDLINE]